Reviewer’s report

Title: Reduced transcription of TCOF1 in adult cells of Treacher Collins syndrome patients

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Reviewer: Paul Trainor

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The authors perform case studies involving patients with Treacher Collins syndrome (TCS) and initially identify a number (8) of new and previously unreported pathogenic mutations. Through isolation of leukocytes and mesenchymal cells from individual adult patients the authors confirm through RT-PCR that TCOF1 haploinsufficiency is associated with TCS. Furthermore the inability to detect certain mutated alleles are suggestive of the occurrence of nonsense mediated decay. These two characteristics of TCS were fairly well established already but this data observed in adults provides good substantiative evidence.

-Major compulsory revisions

The major issue arising from this paper however is the lack of any relevance for TCOF1 haploinsufficiency during adult life. The authors note, the prognosis for mandibular distraction in TCS patients is often poor and hypothesise this could be connected to a stem cell deficit. However there is no evidence to back up these claims and thus no significance can be attributed to adult haploinsufficiency. The authors should take their patient specific mesenchymal cell populations and differentiate them into cartilage and bone in culture and assess the capacity of these cells to proliferate, survive, apoptose as well as their efficiency to form chondroblasts, chondrocytes, osteoblasts, osteoclasts etc. If adult haploinsufficiency is relevant there should be noticeable differences between TCS mesenchyme versus control mesenchyme.

-Minor essential revisions.

The reference to the Dixon et al 2006 paper is incorrect when it quotes a high incidence of cell death in neural crest cells. The apoptosis is occurring in the neuroepithelium and not in the neural crest. My understanding is that with respect to the neural crest these cells only displayed reduced proliferation compared to wild type neural crest cells.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a
statistician.

**Declaration of competing interests:**

I declare that I have no competing interests